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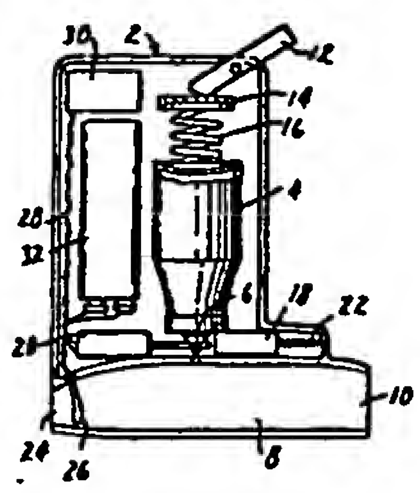
(54) Title: INHALATION DEVICE

(57) Abstract

A portable, battery operated, inhalation device for administration of medicament in the form of aerosolised fine particles or droplets of liquid or suspension to the respiratory system of a patient, the device comprising a housing defining a chamber in communication with a patient port in the form of a mouthpiece or nasal adaptor, medicament aerosolisation means for forming an aerosol of medicament in the chamber, control means to actuate the medicament aerosolisation means and a sensor which measures the air flow rate during respiration through the patient port and provides an electrical signal to the control means which varies continuously with said flow rate, said electrical signal being used by the control means for one or more of the following functions: (i) to calibrate the device such that the medicament aerosolisation means is actuated at a precise, pre-determined flow rate, (ii) to monitor one or more of the following parameters: (a) flow rate at different times during respiration, (b) rate of change of flow rate during respiration, (c) respired volume during respiration, and activate the aerosolisation means when a pre-determined inspiration parameter is attained.



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INHALATION DEVICE

This invention relates to an inhalation device for administration of medicament in the form of aerosolised solid particles or droplets of liquid or suspension. In particular the invention relates to such devices which are actuated to dispense medicament in response to the patient's inspiration.

Asthma and other respiratory diseases have long been treated by the inhalation of appropriate medicament. For many years the two most widely used and convenient choices of treatment have been the inhalation of medicament from a drug solution or suspension in a metered dose pressurised inhaler (MDI), or inhalation of powdered drug generally admixed with an excipient, from a dry powder inhaler (DPI).

Inhalation activatable dispensers for use with aerosol containers which contain medicament and are pressurised with liquid propellants and are equipped with a metering valve through which a plurality of metered doses may be dispensed are known, their general purpose being to afford proper co-ordination of the dispensing of a dose of medicament with the inhalation of the patient thereby allowing the maximum proportion of the dose of medicament to be drawn into the patient's bronchial passages. Examples of such dispensers are described in British Patent Specification Nos. 1,269,554, 1,335,378, 1,392,192 and 2,061,116 and United States Patent Nos. 3,456,644, 3,456,645, 3,456,646, 3,565,070, 3,598,294, 3,814,297, 3,605,738, 3,732,864, 3,636,949, 3,789,843 and 3,187,748 and German Patent No. 3,040,641.

European Patent No. 147028 discloses an inhalation activatable dispenser for use with an aerosol container in which a latch mechanism releasing vane is pivotally mounted in an air passage between an aerosol outlet valve and a mouthpiece, which latch mechanism cannot be released if force to activate the dispenser is not applied before a patient inhales.

The dispenser generally comprises a housing having a mouthpiece and an air passage therethrough terminating at the mouthpiece, the housing being adapted to receive an aerosol container and having a support block with a socket adapted to receive the stem of the valve of the aerosol container and a through orifice communicating between the socket and the air passage, and latch means having parts movable between an engaged position in which movement of the container and the support block toward each other upon the application of a force to bias the container and the support block toward each other is prevented and a release position in which movement of the container and the support block toward each other in response to said force is permitted causing the stem to move to its inner discharge position, the latch means comprising a vane mounted on the housing in the air passageway between the orifice and the mouthpiece for movement toward the mouthpiece under the influence of inhalation through the mouthpiece to release the latch means in which the vane moves toward the mouthpiece from a blocking to a non-blocking position with respect to the passageway in response to inhaling at the mouthpiece and releases the latch means only during the application of said force to bias the container and support block toward each other.

This inhalation device has been received favourably by patients and doctors since it not only overcomes the hand-lung co-ordination problem but it does so at a very low triggering flow-rate (approximately 30 litres/minute) essentially silently, and with a very compact design barely larger than a standard inhaler.

U.S. Patent No. 4,648,393 discloses an electrically-operated metered-dose inhaler in which a mechanical valve blocking means is withdrawn by the action of a solenoid moving in response to the closing of a switch; the switch constitutes an electromechanical breath-actuation means which responds to inhalation by the patient. WO87/04354 discloses a medical dosing device for discharge of medicament for inhalation which comprises a handheld

holder for a medicine container from which medicine is discharged via a valve into an air channel for inhalation by means of initiation of an activation device. The valve is operationally connected with a control unit arranged on initiation of the activation device to control the discharge valve for intermittent opening and closing repeatedly within an inhalation period. The control unit is an electronically controlled unit which activates an electrically controlled discharge valve.

In both cases the inhalation detection is achieved by electromechanical means, involving the rotation of a vane in response to inhalation and the use of this vane to close an electrical switch.

A letter by T J Coady et al. to British Medical Journal (1976, 1 page 833) describes a standard pressurised aerosol modified to provide an electrical analogue of the release of the dose and of inspiration. The separate signals were fed to a two-channel recorder for study of the patient's inhalation technique. A paper by P J Chowienczyk et al. published by the British Thoracic Society (Summer Meeting, July 13-15th 1988, University of Newcastle upon Tyne: 36, Abstract No. P30) describes a placebo inhaler with a flow sensor, also used to assess patient inhaler technique. Neither of these devices control the release of medicament.

"Deposition and effects of Inhalation Aerosols", S.P. Newman, Dept of Thoracic Medicine, Royal Free Hospital, (1983) discloses an automatic computer-controlled aerosol inhalation system in which a standard pressurised aerosol was connected in series with a Fleisch size 2 heated pneumotachograph and an actuator comprising a computer controlled solenoid operating system. The differential pressure signal from the pneumotachograph was fed to a 10mm H_2O pressure transducer and then amplified (SE Laboratories Electro-Medical Multi-Channel Amplifier system). The flow rate signal was fed via a matching amplifier to the Analogue-to-Digital Convertor (ADC) of a Varian V-77 200 computer, which was also equipped with a 32K word central processor

unit and storage facilities on both magnetic tape and disc. A 50kHz clock pulse was supplied to the ADC from a high frequency oscillator, enabling it to sample flow rate readings every 5 msec. The flow rate signal was integrated by the computer to give inhaled volume, and the aerosol canister could be actuated during the course of inhalation by a solenoid mounted on top of the aerosol actuator, the lung volume for firing the aerosol being preset at any desired percentage of vital capacity by a computer programme written in Fortran. Communication was maintained with the computer via a Hazeltine visual display unit and keyboard. The automatic aerosol inhalation system is not portable and is confined to hospital use.

Dry powder inhalers in which the medicament is introduced into the device from a capsule are disclosed in U.S. Patent Nos. 3,948,264, 3,971,377 and 4,147,166 and British Patent No. 1479283. Dry powder inhalers having a reservoir of dry powder from which unit doses are transferred to a chamber by means of a delivery system, such as a rotating perforated membrane in which the perforations are filled with powder from the reservoir, are disclosed in British Patent Application Nos. 2102295 and 2144997 and European Patent Application Nos. 69715, 79478 and 166294.

U.S. Patent No. 4,735,358, European Patent Application No. 239802 and British Patent Application Nos. 2108390, 2122903 and 2166957 disclose vaporisers in which active substances capable of modifying the local atmosphere e.g. insecticides, deodorants and aromatics are vaporised for dispersion to the atmosphere. The active substance is carried or impregnated on a belt or tape consisting of a suitable base material, in such a state that vaporization can be conducted at ambient temperature or under administration of localised heating by a vaporising head. The substance is maintained in an inactive condition until the belt passes over the vaporising head whereby thermal release is achieved. The belt may be moved to the vaporising head by hand or

at a fixed speed by a motor driving feed means through a reduction gear and is taken up by a shaft or spindle. In one embodiment the belt is contained in a cassette to provide a re-usable device, the cassette being engaged by drive means and having a suitable aperture for the belt to pass across the vaporising head. None of the vaporisers disclosed are suitable for delivering a predetermined unit dose of powdered solid medicament to a patient.

Our co-pending International Patent Application No. PCT/US90/02412 discloses a dry powder inhalation device comprising a housing defining a chamber in communication with a patient port in the form of a mouthpiece or nasal adaptor, and an elongate carrier bearing a powdered medicament, the device being constructed and arranged such that areas of predetermined size of the elongate carrier may sequentially be exposed within the chamber, the device comprising one or more air inlets such that when a patient inhales through the patient port an air flow is established from the air inlet(s) to patient port through the chamber such that particles of the powdered medicament of respirable size from said exposed area of the elongate carrier are entrained within the air flow.

The powder inhaler is capable of delivering multiple, uniform doses of a medicament to a patient and is simple to operate and does not require the patient to insert capsules of medicament or rely upon a separate reservoir of medicament in order to load the device for use. The medicament is preloaded on an elongate carrier, sections of which are passed sequentially into the chamber for dispensing the medicament. The elongate carrier may be conveniently loaded on a spool (in a similar manner to a photographic film) or in a cassette (in a similar manner to an audio cassette). The elongate carrier may have any ratio of length : width but is preferably greater than 5 : 1, more preferably greater than 50 : 1 and more preferably between 100 : 1 and 1000 : 1.

A preferred device of this type includes means for releasing medicament from the carrier during inhalation triggered in response to the patient inhaling in order to avoid the patient having to synchronise inhalation and actuation of the release mechanism. Airflow detection may conveniently be accomplished by means of a movable vane positioned within the chamber or patient port, motion of the vane causing actuation of the release mechanism. Such a vane may also be constructed to prevent a patient exhaling through the device and/or preventing exhaled air from reaching the stored carrier thereby avoiding any problems associated with moisture.

It has now been found that the use in a breath-actuated inhaler of a sensor which continuously measures the air flow rate during respiration and provides an electrical signal which varies continuously with flow rate provides significant advantages compared to the inhalation detector system employed in the prior art inhalers.

Therefore according to the present invention there is provided a portable inhalation device for administration of medicament in the form of aerosolised fine particles or droplets of liquid or suspension to the respiratory system of a patient, the device comprising a housing defining a chamber in communication with a patient port in the form of a mouthpiece or nasal adaptor, medicament aerosolisation means for forming an aerosol of medicament in the chamber, control means to actuate the medicament aerosolisation means and a sensor which measures the air flow rate during respiration through the patient port and provides an electrical signal to the control means which varies continuously with said flow rate, said electrical signal being used by the control means for one or more of the following functions:

(i) to calibrate the device such that the medicament aerosolisation means is actuated at a precise, pre-determined flow rate,

(ii) to monitor one or more of the following parameters:

(a) flow rate at different times during respiration,

(b) rate of change of flow rate during respiration,

(c) respired volume during respiration, and activate the medicament aerosolisation means when a pre-determined inspiration parameter is attained.

The devices of the invention may be of the dry powder type, pressurised aerosol type or contain other aerosol generators. The devices of the invention are portable, pocket-size, battery operated devices which may continuously accompany patients such as asthmatics who may need medication at any time.

The present invention extends the use of electrical sensing in breath-actuated inhalers beyond simply detecting the presence of air flow and using that to initiate electromechanical actions. In the device of the invention the sensors continuously measure the air flow rate and the control means utilises the signals derived from the continuous measurement in a number of possible ways. Such sensors may take the form of flow sensors, e.g., those which measure the cooling effect of an air flow or those which measure the speed of rotation of a turbine in the air stream, or may incorporate pressure differential transducers, which sensors may be associated with mechanical, hydraulic, pneumatic (e.g. Pitot tubes) or other linkages to increase their sensitivity. The essential characteristic of such sensors is that they have an electrical output which varies continuously with flow rate.

The output from the sensor, which may be linearised, is fed to either an analogue comparator

circuit or to digital electronics, depending upon the degree of sophistication of its intended use, which may include the following:

(A) <u>Use of continuous flow measurement sensors to facilitate accurate calibration of individual devices</u>.

Electromechanical inhalation detection sensors of the kind already known in the prior art of inhalation devices operate an electrical switch at a preset flow value determined by the mechanics of the system. Manufacturing variance in the mechanical components may result in a substantial device-to-device variability in the flow rate at which the sensors trigger, and, once manufactured, no adjustment is generally possible. The use of continuous measurement sensors in accordance with the invention facilitates the individual calibration of inhalation devices, so ensuring a very small device-to-device variation in actual triggering flow rate. Such calibration may be as simple as the manual adjustment of a potentiometer during manufacture, or it may be a fully automated part of the manufacturing process. In the latter case, the use of digital electronics is highly advantageous, permitting calibration to take the form of insertion of an individually determined calibration factor into memory.

For example, an inhaler which uses a continuous sensing flow-transducer for single point detection of triggering flow and has the facility for factory calibration of the flow sensor output using analogue electronics may have the following arrangement:

1. The air flow generated by the patient's inhalation is detected by the flow-transducer, which comprises one of the continuous sensing types described herein. The transducer produces a voltage output, Vt, which depends on the inhalation flow rate.

2. The flow-transducer output voltage, VT, is adjusted by a pre-set calibration potentiometer to give a calibrated voltage output, Vc.

3. The calibrated voltage, Vc, is fed to an analogue voltage comparator and associated logic circuitry. The comparator compares the input voltage, Vc, with a constant reference voltage. The latter voltage is fixed at a level corresponding to the calibrated output which would be produced by the flow-transducer at the triggering flow rate specified for the device.

4. If the inhalation flow rate equals or exceeds the specified triggering flow rate, and hence Vc equals or exceeds the standard reference voltage, an output is obtained from the analogue comparator. This, in turn, results in an output from the associated logic elements which drives the electromechanical actuation mechanism and so actuates the aerosol valve, delivering a dose of medication to the patient's lungs.

A production calibration facility for use with such an inhaler having analogue electronics may be arranged as follows:

1. A reference air flow rate is generated by a flow generator consisting of a servo pump. This airflow is measured by a reference flow-transducer, which may consist of a Fleisch pneumotachograph.

2. The reference airflow is pulled from the mouthpiece of the inhaler being calibrated and the voltage output from the device's flow-transducer, scaled by its calibration potentiometer (Vc), is fed to the voltage comparator of the calibration facility.

3. The calibrated output Vc is compared with the voltage output from the reference flow-transducer, Vrt, in the comparator of the calibration facility. This comparator, with its associated logic, produces a voltage output, Vdiff, proportional to the difference between the two input voltages and this is fed to a stepper motor driver.

4. The stepper motor, which is mechanically coupled to the potentiometer in the inhaler under calibration, adjusts the potentiometer by an amount proportional to the output from the comparator (and hence, proportional to the calibration error).

5. If a voltage difference (and hence, calibration error) continues to be detected by the comparator, the calibration facility continues to make finer adjustments to the inhaler's potentiometer setting until correct calibration results in a zero Vdiff.

An inhaler which uses a continuous sensing flow-transducer for single point detection of triggering flow and incorporates digital electronics and has the facility for production calibration of the flow sensor output using digital electronics may have the following arrangement:

1. The air flow generated by the patient's inhalation is detected by the flow-transducer, which comprises one of the continuous sensing types described herein. The transducer produces a voltage output, Vt, which depends on the inhalation air flow rate.

2. The voltage Vt is fed to an analogue to digital converter which outputs a digital representation of this analogue input into a digital comparator and associated logic elements.

3. The comparator compares the digital value representing Vt with a stored digital value supplied from the inhaler's memory. If the former value equals or exceeds the latter, a suitable drive output is generated. The stored digital value represents the specified triggering flow rate of the inhaler.

4. The drive output is fed to the electromechanical actuation mechanism, which then operates to actuate the aerosol valve, so delivering a dose of medication to the patient's lungs.

A production calibration facility for use with such an inhaler having digital electronics may be arranged as follows:

1. A reference air flow rate is generated by a flow generator consisting of a servo pump. This air flow is measured by the reference flow-transducer, which may consist of a Fleisch pneumotachograph.

2. The reference air flow is pulled from the mouthpiece of the inhaler being calibrated and the voltage, Vt, from the inhaler's flow-transducer is fed, via an analogue to digital converter to the microprocessor of the calibration facility.

3. The voltage output from the reference flow-transducer is converted to a digital output, which is also fed to the microprocessor.

4. The microprocessor compares the two input values and computes the value which would be obtained from the inhaler at the specified triggering flow rate for the device.

5. The computed value is stored in the inhaler's memory for use by its comparator in determining the inhalation triggering point.

The above arrangements have advantages over the known prior art in terms of their potential for greatly reducing device-to-device variation in actual triggering flow rates by facilitating calibration of individual devices.

Those inhalation sensors of the types disclosed which have no frictionally moving parts would also have the advantage of being much less susceptible to changes in use due to contamination or wear of surfaces, etc.

(B) Detection of increasing flow rate

Detection of an increasing inhalation flow rate and its passage through two precise, pre-determined values within a given time period (Tmax) may be required before firing of the aerosol is triggered, so ensuring that, if the patient falters in their inhalation, the inhaler will not be triggered. A variant upon this method of use, should it be necessary to initiate the firing sequence as

early in the inhalation as possible, is to initiate the sequence as soon as the lower threshold is detected but abort the sequence if the upper threshold has not been reached just prior to actuation of the drug delivery means.

An inhaler which requires the detection of dual threshold flow rate values having analogue circuitry may be arranged as follows:

1. A flow-transducer, comprising one of the continuous sensing types described herein, detects and measures the inhalation flow rate and outputs a voltage, Vt, (which depends on the flow rate) which is fed to an analogue comparator and appropriate logic circuitry.

2. When the comparator detects that Vt has reached, or exceeded, a constant reference voltage, Vr1 (which equals the voltage output which would be produced by the flow-transducer at the lower threshold flow rate), (F1), the timer is started. This timer is pre-set to run from a time Tmax, the maximum permitted time for the attainment of the upper threshold flow rate value, (F2), to a time zero (T=0).

3. If the comparator detects that Vt has reached the second constant reference voltage, Vr2 (which equals the voltage output which would be produced by the flow transducer at the upper threshold flow rate, (F2), before the timer reaches zero, a suitable output is sent to the electromechanical actuation module and an 'OK' indication is provided by means of a suitable display.

4. If the timer times out (the timer reaches zero) before the comparator has detected that Vt has reached Vr2, no actuation output is produced and a 'FAIL' indication is set.

5. If Vt reaches Vr2 before the timer reaches zero, resulting in an actuation output, the electromechanical actuation module operates and the aerosol valve is so fired, delivering medication to the patient's lungs.

An inhaler which also operates on the flow detection criteria but which employs digital circuitry may be arranged as follow:

1. A flow-transducer, comprising one of the continuous sensing types described herein, detects and measures the inhalation flow rate and outputs a voltage Vt (which depends on the flow rate) to an analogue to digital converter.

2. The digitised value of Vt is then fed to a microprocessor.

3. A microprocessor compares the digital value of Vt with a value, held in memory, which represents the lower threshold value (F1) for inhalation flow rate. When it detects that Vt has reached this value it begins measuring the elapsed time before the upper threshold flow rate value (F2) (also held in memory) is reached. It may, or may not, at the point of detection of the lower threshold value, output a signal to the electromechanical actuation module to initiate actuation of the aerosol valve.

4. The microprocessor then monitors Vt, looking for the attainment of a value not less than that of the second value, held in memory, which represents the upper threshold flow rate (F2) for triggering of the inhaler. If this event is detected before the timer reaches zero, the microprocessor sends (or maintains) a suitable output to the electromechanical actuation module, enabling it to actuate the aerosol valve.

5. If the timer reaches zero before the second threshold is detected, no output is sent to the actuation module (or the output is removed prior to the completion of actuation) and the triggering sequence is aborted.

The arrangement provides a major improvement in breath-actuation by ensuring that a dose of drug is only delivered if the patient inhales steadily. Initiation of the breath-actuated triggering sequence could be set off

by the detection of the start of inhalation (using a very low first threshold value), but if the patient falters in their inhalation and the second higher threshold value is not achieved (possibly within a preset time limit), the firing sequence could be aborted without drug release. Alternatively, drug might be released but the patient then warned that delivery to the lungs may not have been fully effective.

(C) Detection of a changing inhalation flow rate and the rate of its change (ramp)

If the rate of change is not within a preset window then the actuation sequence is not commenced.

An inhaler which is triggered according to such control criterion may be arranged as follows:

1. A flow-transducer, comprising one of the continuous sensing types described herein, detects and measures the inhalation flow rate and outputs a voltage, Vt (which depends on the flow rate) to an analogue to digital converter.

2. The digitised value of Vt is fed to a microprocessor.

3. The microprocessor computes the rate of inhalation flow rate change over fairly short (relative to the duration of an inhalation) but finite time intervals and compares this with the limits set for the flow rate ramp window (held in memory). This operation is constantly repeated throughout the inhalation until the inhaler has been actuated or the inhalation has been 'FAILED'.

4. If the flow rate ramp data fall within set criteria held in memory, a suitable output is provided to the electromechanical actuation unit, causing it to actuate the aerosol valve and deliver a dose of medication. An 'OK' indication is also set.

5. If the flow rate ramp data falls outside the set criteria, the inhalation is failed as being unsuitable for satisfactory deposition of drug in the lungs, actuation of the inhaler is aborted and a 'FAIL' indication is set.

This arrangement facilitates optimisation of drug delivery to the lungs by ensuring that drug is only released if the rate of change of inhalation flow rate is within the optimum 'window'. If the rate of change were outside of the defined limits, the breath-actuation sequence would be aborted; alternatively, drug release might be permitted but the patient warned that drug delivery would have been sub-optimal. This feature would be of particular value in the case of too rapid an increase in flow rate, such that the flow rate at the time of actual inhalation of the drug would be so high as to result in a very high degree of impaction of drug in the upper airways and little penetration of the lower airways.

(D) <u>Detection of inhalation and integration of the measured flow rate over time to determine the inhaled volume</u>

The device is triggered when a preset inhaled volume is reached, providing a more direct method of ensuring that triggering occurs at a preset, ideally early, point in the inhalation. Volume measurement could, readily, be used in conjunction with dual threshold or ramp detection to further improve the degree of control.

An inhaler which is triggered according to such control criterion may include the following arrangement:

1. A flow-transducer, comprising one of the continuous sensing types described herein, detects and measures the inhalation flow rate and outputs a voltage, Vt, (which depends on the flow rate) to an analogue to digital converter.

2. The digitised value of Vt is fed to a microprocessor.

3. The microprocessor monitors the inhaled volume by integrating flow rate over time and compares this volume with a pre-set value of triggering volume held in memory.

4. If the inhaled volume reaches the pre-set value (within any pre-set time limit also held in memory), a suitable output is provided to the electromechanical actuation unit, enabling it to fire the aerosol valve, and an 'OK' indication is set.

5. If the patient should fail to inhale the pre-set volume (within any pre-set time limit), the inhalation is 'FAILED' as being unsuitable for satisfactory deposition of drug in the lungs, actuation of the inhaler is aborted and a 'FAIL' indication is set.

This arrangement is advantageous in that it is just as important to deliver the drug very early in the inspiration as it is to deliver it at a low inspiratory flow rate. Whilst triggering by means of detection of a low threshold flow rate might satisfy both the above criteria, use of inhaled volume measurements for triggering would provide more certain and direct control and would aid in optimising performance.

(E) <u>Teaching aid</u>

In addition to their use in controlling the triggering of the inhaler, the measurement modes in (B), (C) and (D) could be used to provide a teaching aid for the patient.

Providing a means for the patient to switch off the triggering circuitry, so that the device functions only as a flow sensor, would enable the patient to practice with the device, without drug being delivered, in order to improve their inhalation technique. Indication of their performance could be as simple as a pair of LED indicators, indicating satisfactory or poor technique, or could be more sophisticated with LCD display of actual parameters.

Use of the control modes described, particularly those of (B), (C) and (D) could have substantial benefits in patient eduction if used in a training mode, as in (E). Increased sophistication in inhalation drug delivery devices can only achieve its full potential benefit to the patient if the patient is able to produce a near optimum inhalation manoeuvre on a regular basis; there is little point in preventing release of drug when delivery is predicted to be sub-optimal if this results in the patient sometimes being unable to obtain a dose at all. Consequently, provision of a facility for the patient to practice using the device, without drug delivery but with provision of indication of the acceptability of his performance, would be of considerable importance. Along the same lines, it may be desirable to provide the option of allowing drug delivery under sub-optimal conditions, but with indication of poor compliance, so that the patient can be guided towards better technique without suffering the frustration of being unable to achieve drug delivery at all.

Additionally the flow rate data may be stored in the device and down-loaded to a printer or computer for analysis and evaluation of patient progress. In a particularly sophisticated version of such a device, the sensor may be used to measure respiratory flow rate data including specific expiratory lung function parameters such as:

FEV_1 (forced expiratory volume in 1 second),
PEFR (peak expiratory flow rate),
FVC (forced vital capacity);

and optionally used to control delivery of precise amounts of aerosolised medication in response to inhalation.

The lung function data recorded could be:

(1) logged for subsequent downloading onto a computer/printer for analysis at a clinic,

(2) displayed immediately for the patient to record on a chart and so monitor the trend of the illness with a view to changing the treatment if required,

(3) manipulated electronically to indicate automatically the need for a change in treatment regimen, or to warn the patient to consult a physician, and,

(4) optionally used to control the amount of medication to be dispensed.

It will be appreciated that in the case of a pressurised aerosol, when the aerosol spray is released, there may be a sudden change in the output signal of the sensors, particularly from those sensors which measure cooling effects. The control means may be programmed with the expected profile of the signal change for release of the aerosol spray and compare the actual signal change during release of the aerosol spray with the expected profile to register the occurrence of spray release and/or indicate this to the patient. The control means may also compensate for the effect of the spray release upon the signal from the sensor in order to ensure accuracy of the measurement of the air flow rate.

The invention will now be described with reference to the accompanying drawings in which:

Figures 1, 2 and 3 and 4 illustrate inhalation devices in accordance with the invention, and

Figures 5, 6 and 7 represent block diagrams showing possible modes of operation for the inhalation device of Figures 3 and 4.

Figure 1 represents a diagram of an inhalation device in accordance with the invention which comprises a housing (2) containing an aerosol canister (4) equipped with a metered dose dispensing valve. The valve stem (6) is securely held in a nozzle block (not shown) and the

valve is actuated by downward movement of the aerosol canister. The valve is directed to fire medicament into chamber (8) which is in communication with mouthpiece (10).

The device is primed for use by lever (12) which moves spring guide (14) compressing spring (16) against the base of the aerosol canister (4). Movement of the canister is prevented by blocking member (18). Blocking member (18) is held in position by compressed biasing spring (22) such that when the solenoid (20) is energised the blocking member will be pushed sideways to allow movement of the canister (4) thereby firing the valve.

When the patient inhales through the mouthpiece (10) an airflow is established from air inlet (24) through the chamber (8) to the mouthpiece, which airflow impinges upon flow sensor (26). The signal generated by the flow sensor (26) is conveyed via electrical conductors (28) to an electronic controller (30) which monitors the signal and actuates solenoid (20) at the appropriate time in the inspiration cycle. The electrical circuits are powered by battery (32).

The flow sensor (26) may be a heated resistive element ('hot wire anemometer') exposed to the airflow through the device. The fall in resistance caused by the cooling action of the inspiratory airflow is preferably used to create an electrical output signal by means of a Wheatstone bridge electrical circuit arrangement or similar. The output signal may be used to trigger medicament released and/or record inspiration data as discussed above.

In a variation of this embodiment (not shown), shielding means are provided to effect different degrees of cooling depending on the direction of the airflow, thereby differentiating between inhalation and expiration.

An alternative embodiment utilises the flow sensor (26) in the form of a heated semiconductor junction or thermistor whose impedance is temperature dependent and thus responsive to cooling by an airflow through the device. This type of sensor has the advantage over a hot wire anemometer of increased sensitivity. In addition, such devices may have particularly low thermal mass.

In a further embodiment the flow sensor (26) is in the form of a thermocouple (junction of dissimilar metals) the voltage output of which, being related to its temperature, may be used to provide a measure of the air flow rate in a similar manner to the temperature sensor disclosed for the above embodiments. The other junction of the same two dissimilar metals (commonly called the "cold junction") would be located in a region of the device likely to be stable in temperature over the likely time period for which airflow is to be measured.

In a further embodiment flow sensor (26) comprises a pyroelectric crystal material which is heated by a coil, the crystal being cooled by the airflow thereby modulating the electrical signal generated. The electrical signal may be used for triggering the device, calibration, data generation and storage etc., as described above.

Referring to Figure 2 like parts to the device illustrated in Figure 1 are designated with identical numerals. The device dispenses dry powder which is introduced into the chamber (8) in a capsule (34) via inlet (24), the capsule being ruptured or split by spike (36). In use, the flow sensor (26) detects patient inspiration and the control means (30) actuates vibrator solenoid (38) at the appropriate time which vibrates the capsule (34) releasing powder into the airflow. Screen (40) prevents capsule fragments from reaching the mouthpiece.

In one embodiment of the invention the continuous flow sensing takes the form of a differential pressure transducer (for example of the type disclosed in U.S. Patent No. 4,988,953), which measures the pressure drop between two regions of an inhaler when a patient breathes through the mouthpiece.

Figure 3 shows an inhaler of the invention which has been made by adapting an inhaler commercially available from Minnesota Mining and Manufacturing Company under the registered trade mark AEROLIN AUTOHALER (100) in several ways. Firstly, the air intake openings usually in the bottom of the mouthpiece (101) have been sealed up; secondly, the vane (107) has been modified to remove a substantial portion of the vane such that the blocking action of the mechanism is retained but the vane will not pivot under the influence of inhalation alone, and thirdly, three holes have been made in the plastic case (102) forming the main body. A first hole (103) is towards the top of the aerosol can (104) and a second hole (105) is towards the bottom of the aerosol can (104). Both of these holes (103, 105) lie on the centre line of the inhaler as viewed from the rear and are separated by approximately 15mm.

A third hole (106) is towards the bottom of the device, level with the middle of, or towards the bottom of, the vane. This hole is off-set from the centre line slightly to the right, as viewed from the rear of the device, so as to align with the remaining portion of the vane.

The remaining parts within the Aerolin Autohaler shown in the Figure 3 all perform as in a standard Aerolin Autohaler inhaler attached to a housing or mounting (108), which could be made of aluminium. The housing might preferably have a concave mating surface (109) of the appropriate radius of curvature to form a receptacle for the convex shape of the body (102).

The housing is provided with two through channels (110, 111) which align with the holes (103, 105 respectively) in the body (102). The junction between the concave surface (109) of the housing (108) and the convex surface of the body (102) is such that air passing through the hole (103) must travel along channel (110) and air passing through hole (104) must travel along channel (111). This may be achieved using a sealing layer (112) of some suitable material.

At the ends of each channel (110, 111) is inserted a nipple (127, 128 respectively) onto which a length of flexible tubing (129, 130 respectively) is pushed, making an air tight seal. The two lengths of tubing are connected to the two ports of a differential pressure transducer (132) capable of measuring the pressure drop between the two holes (103, 105) in the body (102) when air flows past them.

Mounted to the underside of the housing (108) is a solenoid (113) attached by means of a bracket (114) and secured by screws (115, 116, 117). The solenoid consists of a plunger (118), coaxial inside a core (119), both having circular cross-section.

The plunger is held against a bracket (120) by a return spring (121), when the solenoid is in the normal (non-energised) condition. The bracket is attached to the solenoid housing (122) by a nut and bolt (123). The bracket (120) constrains the plunger (118) inside the core (119).

The plunger consists of a part (124) with a diameter nearly equal to the internal diameter of the core, which is preferably made of iron or some other strongly magnetic material, and a part with a smaller diameter (125) which is the actuator. The actuator may or may not be made from the same material as the larger part (124) of the plunger, but where it is the same material they are preferably made as one component.

The return spring (121) bears at one end against the solenoid housing (122) and at its other end against the end plate (126) attached to or forming part of the plunger. The plunger itself is constrained by the bracket (120).

The core of the solenoid (124) consists of a large number of turns of a single wire, each turn electrically insulated from the others except along the length of the wire. As shown the wire is wound in three layers but the actual number could be one or more than one. The former onto which the wire is wound (not shown), is normally made from an insulating material e.g. plastic. Each end of the wire is connected to an electrical circuit (not shown). A capacitor (133) is preferably used to energise the solenoid (113), and is in electrical communication with a battery (134), and the electronics circuit board (135). For clarity the electrical connections between the various components are not shown.

Figure 4 shows the outside of the case (131) of Figure 3. Mounted on the case are an LCD display (136), a push button switch (137), two LED's (138, 139) and a single-turn potentiometer (140).

To use the inhaler the patient first shakes the device to mix the contents of the can and then lifts the lever (141) to prime the inhaler in the usual way. Thus a gap (142) is revealed in the top of the inhaler. This serves as an air intake for the purposes of the invention.

Having primed the device the patient then pushes the 'ON' button (137) to activate the electronics, and the capacitor (133) begins to charge from the battery (134). When the capacitor reaches a pre-determined state of charge, or after a pre-determined time delay, a lamp or LED (138) illuminates to indicate that the device is ready. This 'READY' light (138) is preferably green in colour.

As soon as the 'READY' light (138) illuminates, a first timer (not shown) on the circuit board (135) begins to count down from a pre-determined value e.g. 10 seconds defining the 'ready period'. This is the period during which the patient must breath-activate the device.

At the same time a second timer also starts to count down, from a longer time e.g. 20 seconds to define an 'active period'. At the end of the 'active period' the inhaler powers down.

When a patient inhales through the mouthpiece (101), a flow of air is created such that air enters the device through the gap (142) at the top of the inhaler and finds a path around the periphery of the can (104) into the bottom region of the inhaler, where it is free to pass around the modified vane (107) and out of the mouthpiece (101). Unlike in a conventional Aerolin Autohaler inhaler, the vane (107) in the invention does not lift in the presence of a air flow.

It has been found that the pressure difference created between the two measuring positions (103, 105) in the presence of an air flow from inlet to mouthpiece, varies continuously with the flow rate through the mouthpiece (101), in a generally linear fashion between 20 and 100 l/min.

If, as a result of the patient inhaling through the mouthpiece, the pressure difference (and therefore the flow rate) reaches a pre-determined level during the 'ready period', the capacitor (133) is discharged through the coil of the solenoid (119), firing the can to release medicament. The pressure difference, or trigger level is adjustable via the single turn potentiometer (140).

When the solenoid is energised by the capacitor (133) a magnetic field is rapidly created, by solenoidal action, which attracts the large part of the plunger (124) causing it to move against the action of the return

spring (121), which it easily overcomes. Thus the actuator (125) is made to push on the rear of the vane (107) causing it to pivot upwards. As the vane pivots upwards the mechanism operates as it would for a conventional 'Aerolin' 'Autohaler' inhaler and the medication is dispensed into the airstream in the usual way.

If the trigger level is not achieved before the first timer has finished counting down, i.e., during the 'ready period' either because the patient has not inhaled or because they have failed to reach the required flow rate, then the lamp or LED (139) illuminates to indicate that the patient has failed to breath-activate the device. The 'fail' LED (139) is preferably red in colour.

If the patient succeeds in breath-activating the device during the 'ready period', the medicament is dispensed as previously described. At the end of the 'ready period', the lamp or LED (138) is extinguished and the LCD turned on to display the maximum flow rate achieved prior to actuation, i.e., the triggering flow rate. This is displayed until the end of the 'active period' when the second timer has finished counting down. At the end of the 'active period' the inhaler powers down until the next operation of the 'ON' button (137).

If the patient fails to breath-activate the device during the 'ready period' the 'fail' light (139) illuminates. At the end of the 'ready period' the ready lamp or LED (138) is extinguished and the LCD (136) is turned on, but instead of showing the triggering flow rate it displays the maximum flow rate achieved during the 'ready period'. The device powers down at the end of the 'active period' as previously described.

The lever (141) must then be lowered by the patient to reset the mechanism of the inhaler ready for priming

again when next required. Tests with such a device have demonstrated that a consistent triggering flow rate can be achieved at whatever potentiometer setting is chosen.

Figure 5 is a block diagram of an inhaler circuit which uses a continuous flow sensor and analogue electronics to enable the triggering flow rate of the inhaler to be adjusted.

The push button operates an electrical "on" switch (251) which connects the battery (250) to the rest of the circuit via a voltage convertor (252) and starts an initialisation timer (253).

The voltage convertor (252) converts and regulates the 9V d.c. battery to produce +7.5V and -7.5V (nominal) on its output rails. These power rails supply all of the remaining electronic components except the solenoid driver (255) which has a separate power line.

Whilst the initialisation timer is counting down the solenoid driver (255), in the form of a capacitor, is charging up.

When the initialisation timer has reached zero (timed out), two further timers (254, 256) are started, one counts down from 20 seconds (254) and one from 10 seconds (256). At the same time the peak hold circuit (265) is reset and the ready logic (259) illuminates the ready indicator lamp (260) to tell the patient that the inhaler is ready to deliver medicament.

Any flow through the mouthpiece is detected by the pressure transducer (262) which is turned on as soon as the inhaler powers up. The pressure transducer produces an output signal which, when applied to a scaling circuit (263), results in an output voltage proportional to the flow rate through the device.

The scaled output voltage is applied to one side of comparator (264) and the other side of the comparator is connected to a reference voltage. The reference voltage

is adjusted by the set triggering level potentiometer (140) on the outside of the case. The potentiometer can be adjusted to a voltage which corresponds with the output voltage from the pressure transducer (after scaling) at a given flow rate.

The output from the scaling circuit is also applied to the peak hold circuit (265) which updates each time the input voltage exceeds the previous highest input voltage, until a signal appears on its hold input.

The output of the comparator, which changes according to which of the input voltages is the higher, is applied to the pass/fail logic (257).

If the pass/fail logic (257) detects a change in the comparator signal to indicate that the set triggering level has been exceeded and the 10 second timer (256) has not finished counting down to indicate the end of the ready period, then a signal is sent to the solenoid driver (255) to fire the aerosol. At the same time a signal is applied to the hold input on the peak hold circuit to capture the flow rate at which the device is triggered.

When the 10 second timer (256) has finished counting down, the ready circuit (259) is reset and the ready indicator lamp (260) goes out. If the pass/fail logic has not received a signal from the comparator before the 10 second timer (256) has counted down, the fail indicator lamp (258) is illuminated. At the same time the LCD (136) is turned on to display the contents of the peak hold circuit.

If the pass/fail logic indicates a fail situation, the display shows the peak level of flow attained during the ready period. However, if the device was breath-activated during the ready period, the peak hold circuit contains the value which was held at the instant the solenoid was actuated and the display therefore shows the triggering flow rate.

When the 20 second timer (254) reaches zero the electrical "on" switch is reset and the inhaler powers down.

Figure 6 is a block diagram of an inhaler which uses a continuous flow sensor and analogue electronics to monitor flow rate at different times during respiration and activate a pressurised aerosol container.

The push button operates an electrical "on" switch (268) which connects the battery (267) to the rest of the circuit via a voltage convertor (269) and starts an initialisation timer (270).

The voltage convertor (269) converts and regulates the 9V d.c. battery to produce +7.5V and -7.5V (nominal) on its output rails. These power rails supply all of the remaining electronic components except the solenoid driver which has a separate power line.

Whilst the initialisation timer (270) is counting down the solenoid driver (272), in the form of a capacitor, is charging up.

When the initialisation timer (270) has reached zero (timed out), two further timers (271, 273) are started, one counts down from 20 seconds (271) and one from 10 seconds (273). At the same time, the peak detect circuit (310) is reset and the ready logic (276) illuminates the ready indicator lamp (278) to tell the patient that the inhaler is ready to deliver medicament.

Any flow through the mouthpiece is detected by the pressure transducer (280) which is turned on as soon as the inhaler powers up. The pressure transducer (280) produces an output signal which, when applied to a scaling circuit (281), results in an output voltage proportional to the flow rate through the device.

The scaled output voltage is applied to two comparators (279, 282) and a peak detect circuit (310). One comparator (279) has a reference voltage applied to

it corresponding to the scaled output from the pressure transducer at a flow rate of 30 l/min (V ref 1) and the second comparator (282) has a reference voltage applied to it corresponding to the scaled output from the pressure transducer at a flow of 50 l/min (V REF2).

If the output from the 30 l/min comparator (279) changes, indicating that a flow rate of 30 l/min has been achieved, a signal is sent to the counter with hold (277), which starts to count. A voltage signal corresponding to the elapsed time indicated by the counter is constantly applied to the pass/fail logic (274).

If the pass/fail logic (274) detects a change in the voltage from the 50 l/min comparator, indicating that a flow rate of 50 l/min has been achieved, it checks its remaining inputs. Providing that the 10 second timer (273) has not reached zero and the elapsed time indicated by the counter (277) lies in the range 0.1 to 0.5 seconds, a signal will be sent to the solenoid driver (272) to fire the aerosol, at the same time halting the counter.

If the 10 second timer (273) reaches zero or the counter (277) reaches 0.5 seconds the pass/fail logic (274) registers a fail. Similarly if the counter (277) fails to reach 0.1 seconds or the 50 l/min comparator (282) never changes its output, a fail is registered. In the case of a fail, the fail indicator lamp (275) is illuminated.

When the 10 second timer (273) reaches zero the ready logic (276) is reset and the ready light (278) is extinguished. At the same time the display logic (283) turns on the LCD (136) and gets a signal from the pass/fail logic (274) to indicate success or failure. In the case of a pass the display logic (283) gets a value from the counter (277) and the LCD (136) shows the time

between achieving a flow rate of 30 l/min and the device triggering, at a flow rate of 50 l/min. In the case of a fail the display logic (283) gets a value from the peak detect circuit (310) and the LCD (136) shows the maximum flow rate attained during the ready period.

When the 20 second timer (271) reaches zero, the electrical "on" switch is reset and the inhaler powers down.

Figure 7 is a block diagram of an inhaler that uses a continuous flow sensor and analogue electronics to monitor the respired volume during respiration and activate a pressurised aerosol container.

The push button operates an electrical on switch (285) which connects the battery (284) to the rest of the circuit via a voltage convertor (286) and starts an initialisation timer (287).

The voltage convertor (286) converts and regulates the 9V d.c. battery to produce a +7.5V and -7.5V (nominal) on its output rails. These power rails supply all of the remaining electronic components except the solenoid driver (289) which has a separate power line.

Whilst the initialisation timer (287) is counting down the solenoid driver (289) in the form of a capacitor, is charging up.

When the initialisation timer (287) has reached zero (timed out), two further timers (288, 290) are started, one (288) counts down from 20 seconds and one (290) from 10 seconds. At the same time the integrator (299) is reset and the ready logic (293) illuminates the ready indicator lamp (294) to tell the patient that the inhaler is ready to deliver medicament.

Any flow through the mouthpiece is detected by the pressure transducer (297) which is turned on as soon as the inhaler powers up. The pressure transducer (297) produces an output signal which, when applied to a scaling circuit (298) results in an output voltage proportional to the flow rate through the device.

The scaled output voltage is applied to the integrator (299) and a sample and hold circuit (296). The sample and hold circuit (296) updates continually until it receives a signal on its hold line, at which time it stops updating and holds the voltage from the scaling circuit.

The output from the scaling circuit (298) is applied to the integrator (299) where it is summed over time, to produce an analogue voltage signal representative of the total volume of air flowing through the device. The integrated signal is applied to the comparator (295) where it is compared to a reference voltage Vref. The reference voltage is fixed at a level corresponding to the output that would be produced by the integrator after a flow volume of 0.2 litre.

The output from the comparator (295) changes state when the output from the integrator exceeds Vref, this occurs when a volume of 0.2 litres has been measured. At the same time a signal is sent to the sample and hold circuit (296), which captures the signal from the scaling circuit (298) at the instant the 0.2 litres level is exceeded. The pass/fail logic (291) detects the change in the comparator output and providing the 10 second timer (290) has not timed out, it sends a signal to the solenoid driver (289) to fire the aerosol.

If the pass/fail logic (291) does not detect a change in the comparator output before the 10 second timer has timed out, the fail indicator lamp (292) is illuminated to register a fail.

When the 10 second timer (290) reaches zero, the ready logic (293) is reset and the ready indicator lamp (294) is extinguished. At the same time the display logic (301) turns on the LCD (136) and gets a signal from the pass/fail logic (291) to indicate success or failure.

If the signal from the pass/fail logic (291) indicates a pass, then the display logic (301) gets a signal from the sample and hold circuit (296) corresponding to the flow rate attained at the instant the 0.2 litres volume level was exceeded. If the logic indicates a fail then the display logic (301) gets a value from the integrator (299) which will be the total inhaled volume during the ready period.

In either case the value is displayed on the LCD (136) until the 20 second timer (288) has counted down, at which time the electrical "on" switch is reset and the inhaler powers down.

Figures 5, 6 and 7 are block diagrams showing possible modes of operation of the device of Figures 3 and 4. Whilst each mode of operation is shown separately, it will be appreciated that many of the components are common and the device may include a combination of the circuits with suitable switching means to select the desired mode of operation.

CLAIMS

1. A portable, battery operated, inhalation device for administration of medicament in the form of aerosolised fine particles or droplets of liquid or suspension to the respiratory system of a patient, the device comprising a housing defining a chamber in communication with a patient port in the form of a mouthpiece or nasal adaptor, medicament aerosolisation means for forming an aerosol of medicament in the chamber, control means to actuate the medicament aerosolisation means and a sensor which measures the air flow rate during respiration through the patient port and provides an electrical signal to the control means which varies continuously with said flow rate, said electrical signal being used by the control means for one or more of the following functions:

(i) to calibrate the device such that the medicament aerosolisation means is actuated at a precise, pre-determined flow rate,

(ii) to monitor one or more of the following parameters:

(a) flow rate at different times during respiration,

(b) rate of change of flow rate during respiration,

(c) respired volume during respiration,

and activate the aerosolisation means when a pre-determined inspiration parameter is attained.

2. A device as claimed in Claim 1 which comprises a pressurised aerosol container.

3. A device as claimed in Claim 1 which comprises means for introducing dry powder into the chamber.

4. A device as claimed in any preceding Claim which additionally comprises calibration means such that the medicament aerosolisation means can be adjusted to activate at a precise, pre-determined flow rate.

5. A device as claimed in any preceding Claim in which the control means monitors the flow sensor at different times during inhalation and activates the medicament aerosolisation means when two pre-determined flow rates are achieved within a pre-determined time period.

6. A device as claimed in any one of Claims 1 to 5 in which the control means monitors the rate of change of inhalation flow rate and actuates the medicament aerosolisation means at a pre-determined value or within a pre-determined range of values.

7. A device as claimed in any one of Claims 1 to 5 in which the control means monitors the inhaled volume and activates the medicament aerosolisation means when a pre-determined volume is reached.

8. A device as claimed in any preceding Claim in which the control means comprises means for storing and optionally displaying information generated from the sensor.

9. A device as claimed in any preceding Claim in which the control means is associated with means to display or record for future analysis a parameter relating to inspiration or expiration through the patient port, which parameter is generated from the electrical signal from the sensor.

10. A device as claimed in Claim 1 in which the sensor comprises a hot wire anemometer, a thermistor, a heated semiconductor junction, a thermocouple, a heated pyroelectric crystal material, or a pressure differential transducer.

11. A device as claimed in Claim 2 in which the control means is able to compare the sudden change in the output signal of the sensor in response to the release of the aerosol spray to an expected profile of signal change for release of said spray, and where such control means is used to either:

(a) register the occurrences of spray release and/or indicate this to the patient,

and/or

(b) compensate for the effect of said sudden change upon the measurement of the air flow rate.

12. A device as claimed in any preceding claim which additionally comprises means to deactivate that part of the control means actuating the medicament aerosolisation means.

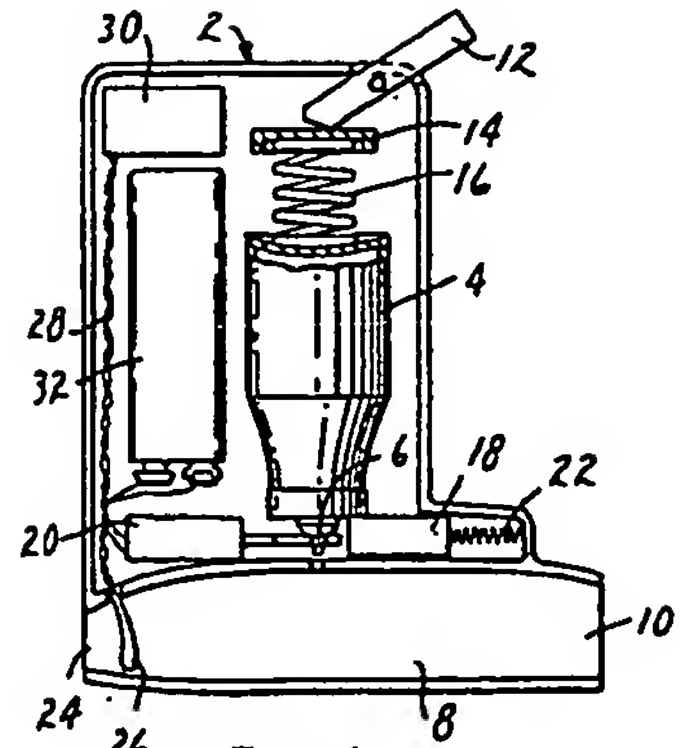

FIG. 1

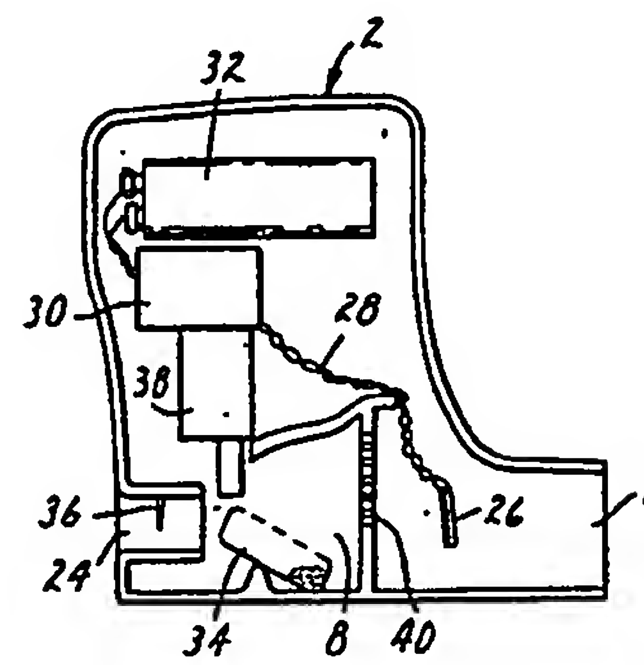

FIG. 2

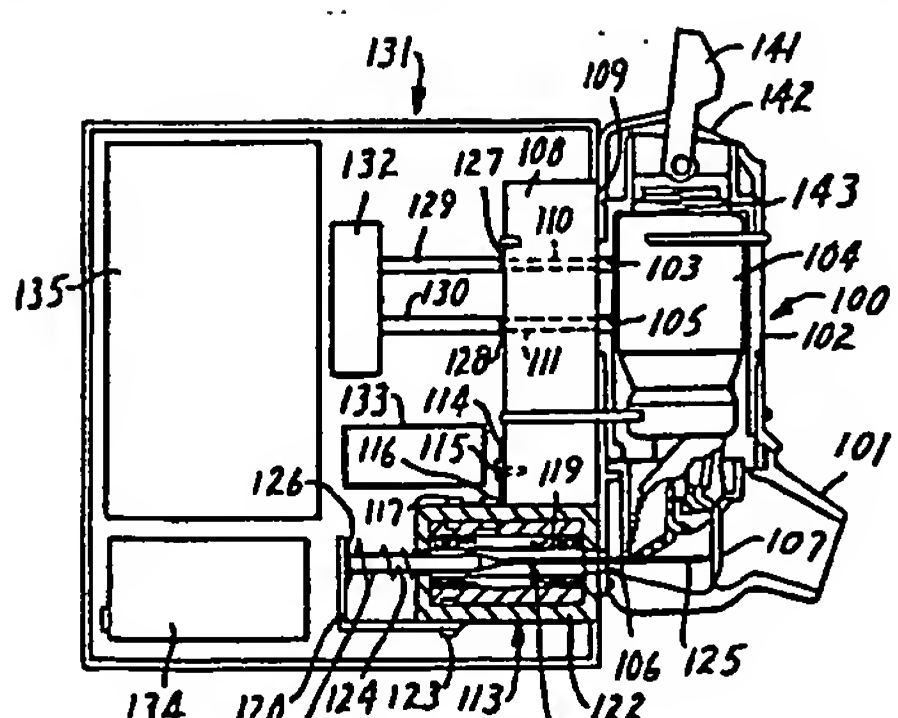

FIG. 3

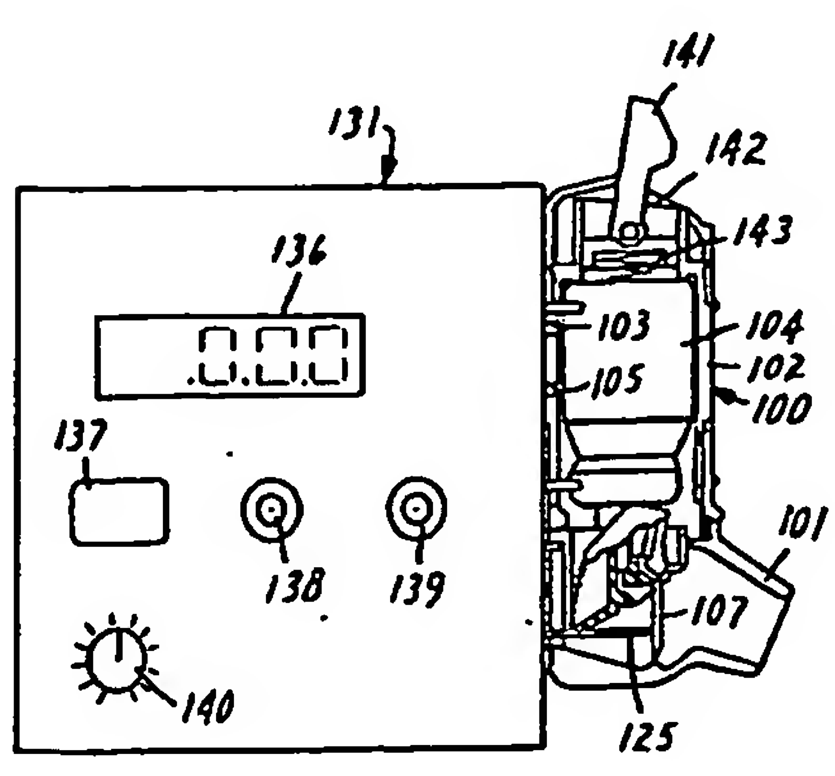

FIG. 4

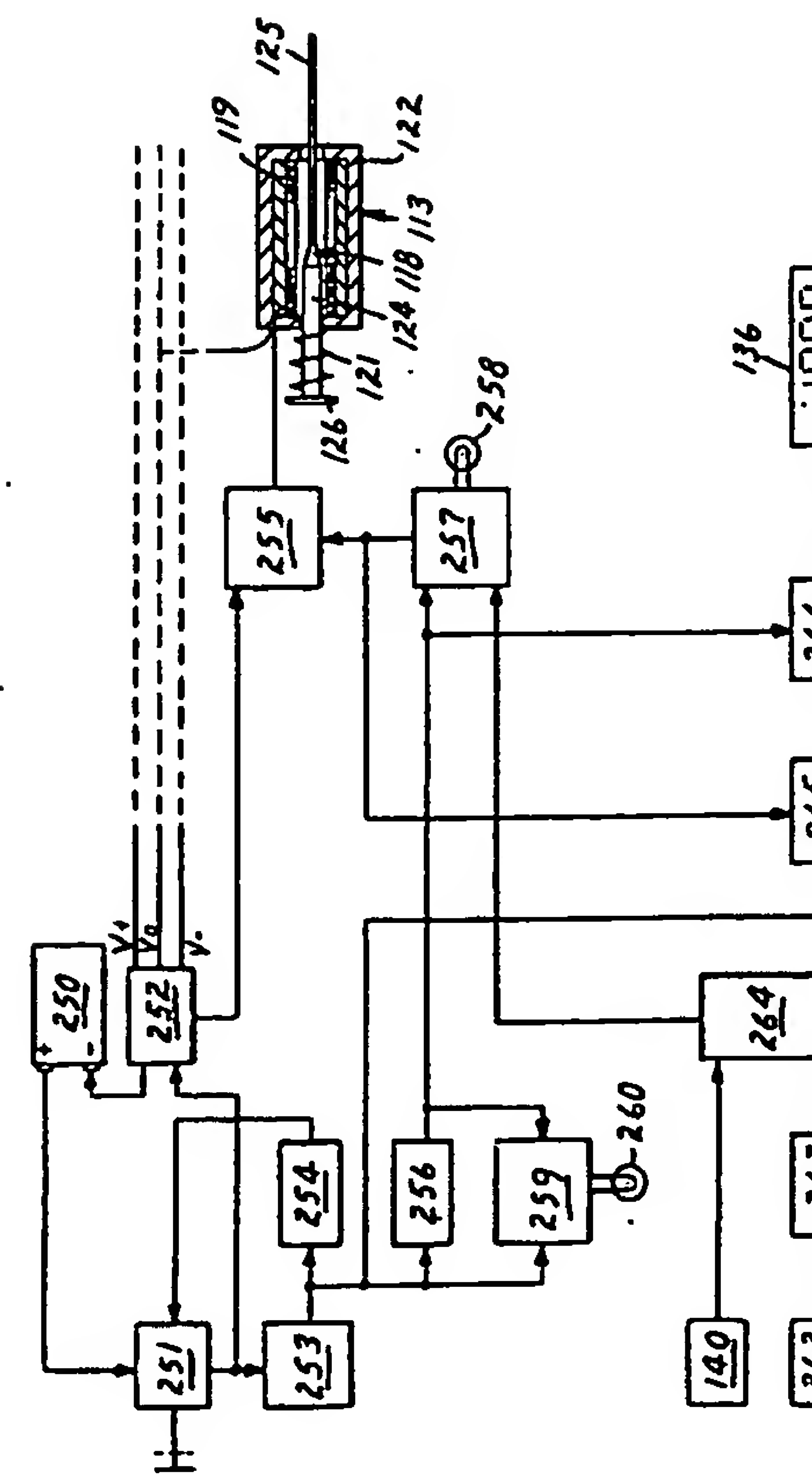

FIG. 5

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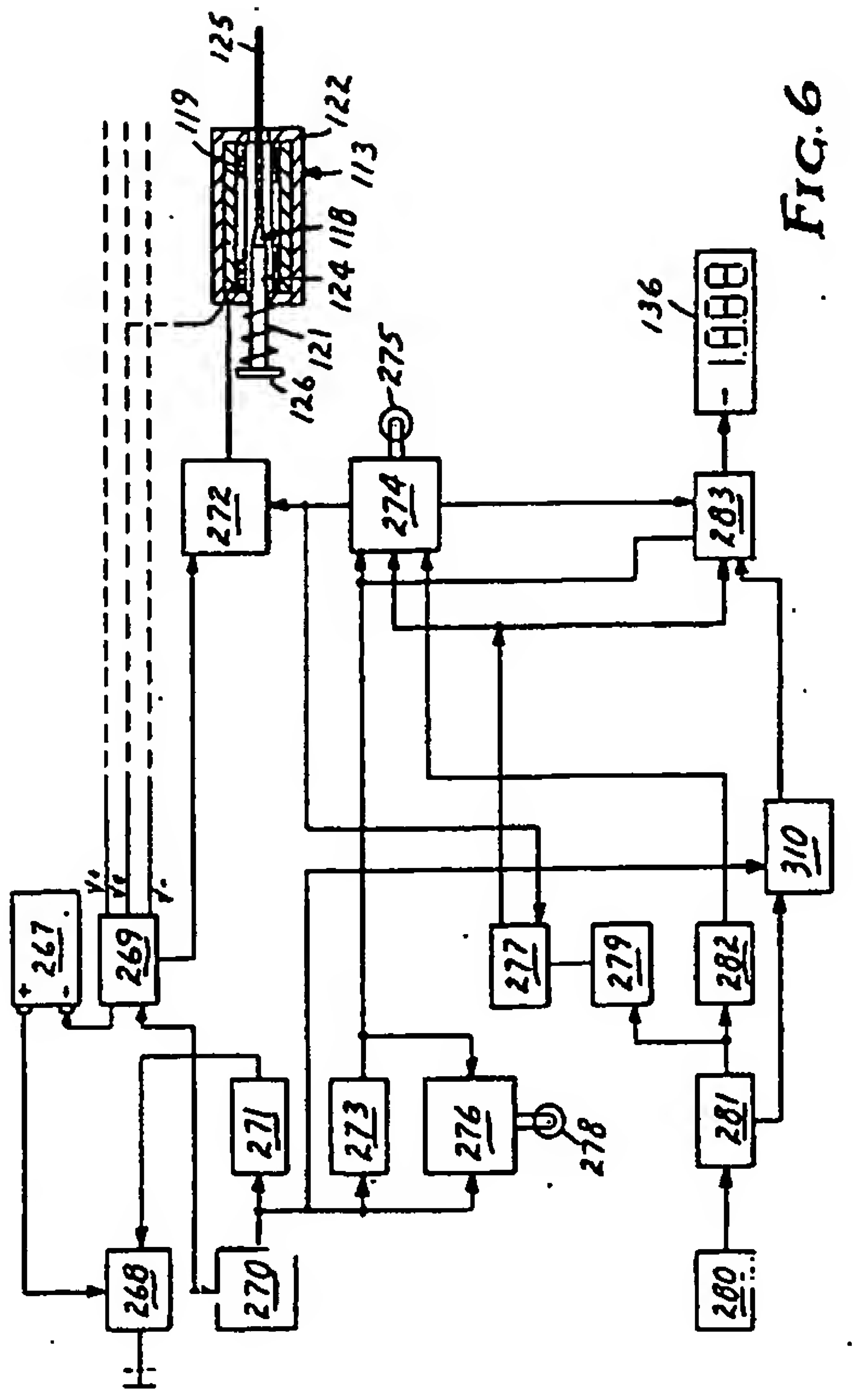

FIG. 6

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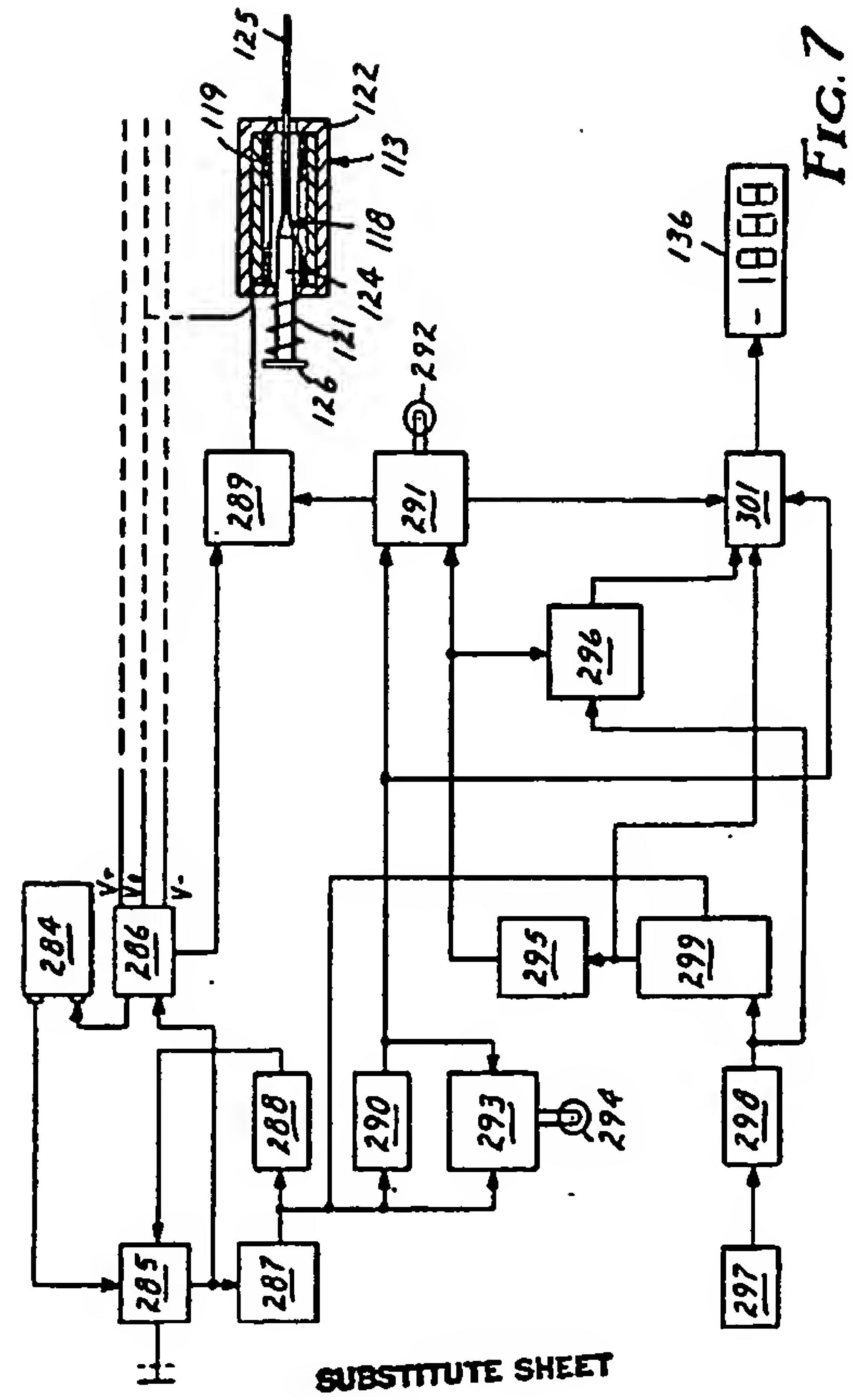

FIG. 7

SUBSTITUTE SHEET

International Application No

I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61M15/00

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
Int.Cl. 5	A61M

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	DE,C,3 901 963 (J SCHATZ) 9 August 1990 see column 6, line 19 - line 25 see column 6, line 34 - line 47 see column 7, line 54 - column 8, line 15 see column 13, line 60 - column 14, line 5 see column 15, line 61 - line 68 see figures 17-19	1,2
X	S NEWMAN 'deposition and effects of inhalation aerosols' 1983 , RAHMS , LUND cited in the application par.:apparatus,programmes see page 26 - page 29	1,2,4, 6-11

-/--

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24 JANUARY 1992	17.02.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VEREECKE A.

PCT/GB 91/01868

International Application No

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	DE,A,2 809 255 (R ROSENTHAL) 14 September 1978 see page 10, line 3 - page 12, line 23 see page 14, line 16 - line 23 see page 16, line 33 - page 17, line 4 see page 18, line 5 - line 12 see figures 1,8	1,4,6, 10,12
A	DE,A,3 617 400 (C HEYER GMBH) 26 November 1987 see column 4, line 1-15 see column 7, line 6-43	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101868
SA 52683

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/01/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-C-3901963	09-08-90	None		
DE-A-2809255	14-09-78	US-A-	4106503	15-08-78
		CA-A-	1095995	17-02-81
		GB-A-	1568808	04-06-80
		JP-A-	53130897	15-11-78
DE-A-3617400	26-11-87	None		

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82